Challenges for Cervical Cancer Prevention in Developing Countries: New Approaches

by

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Abstract

Every year, about 500,000 women worldwide are diagnosed with cervical cancer and among them, more than 250,000 die from the disease. About 80% of these cervical cancer deaths strike young poor women in the developing countries. Due to multiple challenges and barriers, no country in the developing world has managed to initiate and sustain a comprehensive screening program. The purpose of this paper is to discuss new strategies of screening available in low resource countries including visual inspection by acetic acid (VIA), HPV/DNA and careHPV/DNA.

The cytology via Papanicolaou (Pap) smear, the golden standard method of screening during the last decades, has proved unsuitable method of screening in poor regions of the world. Detection of cervical cancer at an early stage is associated with excellent survival but most women in developing countries present with advanced and often untreatable disease. Ongoing efforts to refine the characteristics of the new screening tests continue, as does the implementation of current HPV vaccines for the primary prevention of cervical cancer.

Challenges for Cervical Cancer Prevention in Developing Countries: New approaches

Introduction

Cervical cancer is the second most common cancer in women and a leading cause of mortality worldwide with 273,505 deaths estimated in 2010, similar to the annual number of maternal deaths in childbirth. Eighty-three percent of cases occur in the developing world, where cervical cancer accounts for 15% of female cancers, as compared to just 3.6% in developed countries. [(1)]

Thanks to screening, cervical cancer is not very common in the U.S., with about 12,340 new cases of invasive cervical cancer diagnosed in 2011. [(1)] Unfortunately the same is not true around the world, where more than half a million women are diagnosed with cervical cancer each year. **[(2)]**

In Africa, which has a population of 267.9 million women aged 15 years or greater, it is estimated that 78 897 women are diagnosed with cervical cancer annually and 61 671 (78%) will die from the disease, which is a significantly higher incidence to mortality ratio than found in developed countries. [(1)]

Women in developing countries face a high risk of cervical cancer mortality because their diagnosis is done too late due to the lack of an early screening for the disease. A WHO study in Bangladesh, Ethiopia and Malawi, [(2)] found that less than one percent of women had undergone any form of screening for cervical cancer. In many low income countries, widespread poverty, endemic civil wars and environmental instability make traditional screening programs very difficult.

There is a need to develop alternative strategies to the current screening test for cervical cancer, “the Pap test”, which has proved to be most inappropriate in the developing countries.

For the purpose of this paper, after a short introduction to the biology and the magnitude of the disease in the different regions of the world, and a literature review, I am going to shed light on the main challenges and barriers to the secondary prevention of cervical cancer in low income countries. Also, I will highlight how new screening tests associated with primary prevention could help in alleviating the burden of this disease among women living in poor countries. Finally, I will discuss which conceptual framework can be used to determine the different factors that might positively or negatively influence the uptake of cervical cancer prevention programs in the developing world.

Cervical Cancer Biology

A quick reminder of the anatomy of the uterus is necessary. The uterus is divided into the corpus, the isthmus, and the cervix. The cancer of the cervix originates from the cells of the cervix uteri, the portion of the uterus protruding into the upper vagina.

The vaginal portion of the cervix called portio vaginalis, also known as the ectocervix, is lined by a squamous epithelium and divided into anterior and posterior lips within their center, the external os of the uterine cervix. The external os is connected to the uterine cavity by the endocervical canal or endocervix which is lined by a columnar epithelium. It is important to note that the majority of cervical cancers are called squamous carcinomas (90%) because they develop in the squamous epithelial cells of the ectocervix and more exactly in the Transformation Zone located on the squamocolumnar junction, which is the area separating the two cervical epitheliums lining, respectively, the endocervix and the ectocervix. The remaining cancers (10%), referred to as adenocarcinomas prove more difficult to diagnose due to their location in the endocervical canal.

Cervical cancer is caused by the sexually transmitted common virus called Human Papilloma Virus (HPV). More than 100 strains of the virus exist, but only 15 types have been

consistently linked to cervical cancer. The two most common strains, 16 and 18, cause about 70% of cervical cancers worldwide, whilst strains 6 and 11 are commonly associated with benign genital warts. It is estimated that 60% to 80% of sexually active young people male and female will be infected by HPV at least once during their life time, usually between their late teenage years and their early thirties. Fortunately for most individuals, the immune system will eliminate HPV infection spontaneously without any clinical significance. However, some women are at higher risk for cervical cancer: **(1)**

Those who smoke are about twice as likely as non smokers to get cervical cancer. Researchers believe that tobacco substances damage the DNA of cervical cells and, may contribute to the development of cervical cancer. Smoking also makes the immune system less effective in fighting HPV infection. Women also with frequent genital infections and in particular, HIV infection have a double risk of HPV persistence compared to HIV-negative women with similar risk profiles. They have an impaired immune response usually involving lymphocytes which are reduced in HIV-positive people. This is why cervical cancer is considered as an AIDS-defining illness by the CDC. **(1, 3)**

Cervical cancer is preventable when it is diagnosed in its earliest stages by screening because, as seen above, the disease is largely linked to a viral infection of the lower part of "the uterine cervix'' by HPV, a sexually transmitted agent. It is now well accepted that the persistent infection of the cervix by certain HPVs is a necessary step to the development of cervical cancer. This persistent infection with HPV leads to abnormal cervical cells called cancer precursors or precancerous lesions also known as cervical intraepithelial lesions (CIN).[1]

Detecting cervical cancer precursors has traditionally been done through cervical cytology referred to as a Pap test or Pap smear. The Pap smear has transformed cervical cancer from a leading killer to a rare disease in developed countries. This approach of screening is known as secondary prevention, which means screening women who have already been infected by

HPV, unlike primary prevention which is the vaccination of naïve people without any previous contact with HPV.

The incidence of cervical cancer, as shown by the world map in the appendix, is very high in countries with no national screening program such as those in Sub-Saharan Africa, Latin America, and South-East Asia, where it ranges from 40 to 100/100,000 women. By comparison in the US, the incidence of cervical cancer has been reduced from 56 cases / 100,000 women in the 1940s to 6 cases/ 100,000 women in the 1990s [1, 3]. This has been possible because women with abnormal smears or cancer precursors are referred for colposcopy and biopsy. When the diagnosis of a precancerous lesion is confirmed, the diseased part of the cervix, called the "Transformation zone", is removed by loop excision electrosurgical procedure (LEEP), also known as large loop excision of the transformation zone (LLETZ). This procedure can be performed in an outpatient setting, using a local anaesthetic and relatively unsophisticated equipment. The complication rate of LEEP is low and reported cure rate ranges from 80% to 95%.

Research Methodology

Search strategy

The search included journal articles from January1, 2000, to October 31, 2013. We searched the Cochrane Library and Pub/Med for relevant randomized trials and other high-quality studies: Systematic reviews, meta-analyses for the terms “cervical cancer’’, “cervical carcinoma”, “cervical neoplasia’’,”cervical carcinogenesis” “epidemiology”, “prevention and control”, and ‘’developing countries”. Two hundred sixty seven articles were selected.

Criteria for selecting articles to review

The purpose of this paper is to examine cervical cancer prevention strategies presently used in developing countries. Since the prevention strategies for cervical cancer have tremendously evolved these last years, especially with the coming of the HPV vaccine in 2006 and new tests like HPV/DNA paralleling the resurgence of old tests like Visual Inspection with Acetic Acid (VIA), almost all articles selected are dating from Jan1, 2005. However, older publications of widely known authors that we judged to have remained important were also included. References from relevant articles identified from our search strategy have been retained as well. A total of twenty eight articles have been retained for our bibliography.

Literature Review

Magnitude of cervical cancer in the world

Cervical cancer is the most common cancer among women in developing countries. The public health success which has led to the fall in the number of new cases and deaths from the disease in the developed world, is credited to screening programs. In the developing world, there is little information about rates of screening. To address this lack of information and to estimate the magnitude of inequalities in access to screening services, the WHO in 2008 conducted surveys in 57 countries across all levels of economic development and compared results of:

- The effective coverage: proportion of women who had had a pelvic exam and a Pap smear test in the last three years and
- The crude coverage: proportion of eligible women who reported a pelvic exam regardless of when this occurred.

The researchers found a huge disparity in rates of cervical cancer screening in terms of effective coverage: only 19% of women in the developing world have been screened compared to 63% in the developed countries. For example, 80% of women received effective screening in Austria, compared to 1% or less in Ethiopia, Malawi and Bangladesh. Also, in 16 of the 57 studied countries, 90% of women have never had a pelvic exam. Researchers found as well that poor women who are likely to have exposure to cervical cancer risk factors such as smoking or unsafe sex are less likely to get screened effectively. In developing countries as a whole, screening coverage rates also were declining with advancing age, a risk factor for high incidence rate for cervical cancer [(2)].

Strategies for improving cervical cancer prevention must be adapted to meet the specific needs of individual countries, concluded the WHO report. Expanded screening may be a viable option where sufficient infrastructure and health workforce exist, but novel strategies need to be considered in other settings.

For instance in Africa, which has a population of 267.9 million women aged 15 years and older at risk of developing cervical cancer, approximately 80,372 women are known to be diagnosed with cervical cancer per year, and just over 60,000 women die from the disease, representing the region with the highest burden of cervical cancer in the world with Age Standardized Incidence Rates (ASIR) over 30/100,000 in regions such as East and Western Africa (Globocan Database, 2008). [(3)]

By comparison, in Western Europe, with a total female population of 96 million, there were 9,318 cases of cervical cancer (ASIR of 6.9/100,000) and 3,794 deaths: Age Standardized Mortality Rate (ASMR) of 2.0/100,000 (Globocan Database, 2008). In North America, out of a total female population of 175 million, there were 12,488 cases of cervical cancer (ASIR of 5.7/100 000), with 4,413 deaths (ASMIR of 1.7/100,000) in 2008 (International Agency for Research on Cancer, Globocan Database, 2008). [(3)]

Figure 1 shows the annual number of deaths from cervical cancer in developed and developing regions by age group, and it is evident that the number of deaths in developing countries is nearly 10 times greater than in developed regions.

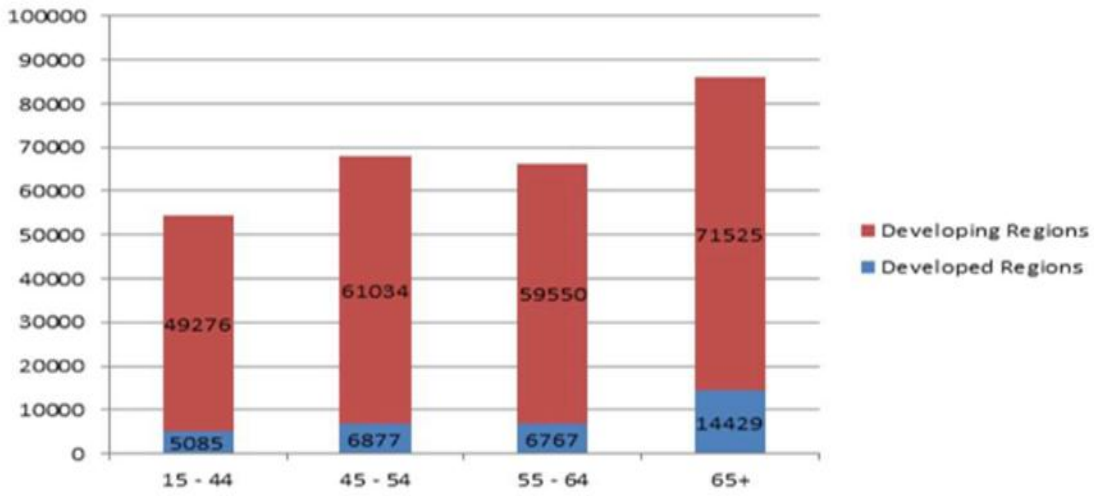

Figure 1. Annual number of deaths from cervical cancer by age group in developed and developing regions (IARC Globocan Database, 2008; Arbyn *et al.*, 2011).

Figure 2 shows the regional variation of incidence and deaths due to cervical cancer in Africa. Of note is the very high incidence and mortality ratio of up to 80% in most regions except Southern Africa (57%) [(3)]

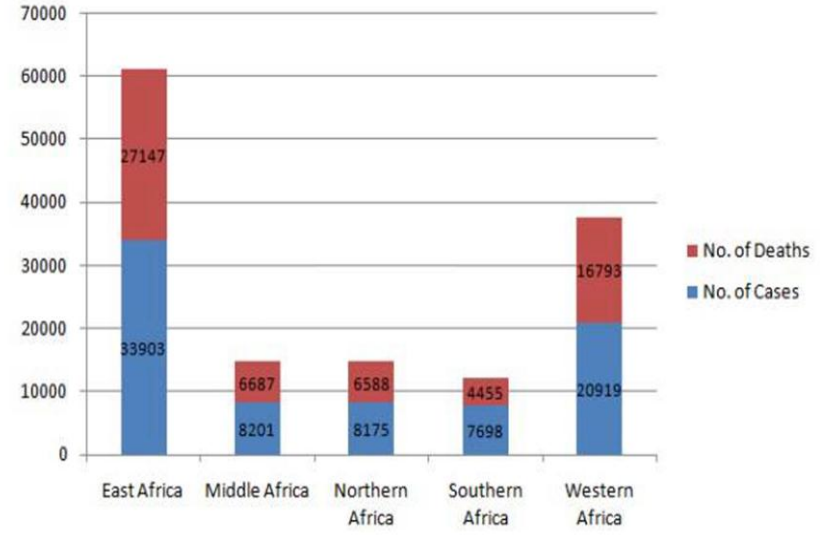

Figure 2. Incidence and mortality from cervical cancer in different regions of Africa (IARC Globocan Database, 2008; Arbyn *et al*., 2011).

Methods of Cervical Cancer Prevention

Cytology or Papanicolaou Test

Cytology or Pap Test/ Smear is the most effective and common screening method. Cervical cytology consists of spreading and staining a smear of collected cervical cells and analyzing them under the microscope to detect precancerous cells. The method enables professionals to accurately detect and stage high grade lesions. This approach can contribute to early detection, thereby decreasing the incidence of advanced cervical cancer and associated mortality.

However, Pap smears are challenging to perform in developing countries because the process requires trained personnel and certified laboratories that are often unavailable [(4)].

Human Papilloma Virus Deoxyribonucleic Acid (HPV/DNA) Test

HPV/ DNA Test is a newer option for cervical cancer screening. The HPV/DNA testing by Hybrid Capture 2 (HC2) consists of screening for high-risk strains of HPV. In some studies,

HPV testing has been shown to reduce mortality with high grade lesions, in advanced invasive cervical cancers and even in women with human immunodeficiency [(5)].

The HPV/ DNA test has shown promising results with high sensitivity and specificity to detect high grade lesions, and therefore it is used as a primary screening test in women aged 30 years or older. The testing is done either with cervical or vaginal samples collected with a brush by a trained provider in the case of cervical screening or by the woman herself in the case of the vaginal sample. The sensitivity of HPV/DNA testing ranged from 66% to 95% for all women tested, but most studies indicated a sensitivity of 85% among women 30 years old or greater [(6)].

However, there are some limitations: the test is expensive, requires a laboratory, and the time needed to process the test is at least 7 hours. Although suitable for low resource settings because it is easy to practice, it requires a sophisticated laboratory to read the samples. Unfortunately, most developing countries do not have reliable laboratory facilities [(4)].

The alternative to HPV/DNA testing is *careHPV*. This moderated HPV test was developed by Qiagen Gaithersburg Incorporated Laboratories in collaboration with the Bill and Melinda Gates Foundation and the Non-Governmental Organization PATH. The test is simple and rapid; the results can be produced within 2.5 hours or less. A portable compact unit with a battery is operated by workers with minimal laboratory training. The test does not require a refrigerator, electricity, or running water.

In the case of care HPV testing, HPV infection is detected with cervical or vaginal swabs and the woman can collect the sample herself. The method was tried in China for the first time and it showed reasonably promising results for the future. [(5)]

The sensitivity of care HPV testing in China was 90% compared to Visual Inspection with Acetic Acid and Pap smear at 41% and 85% respectively. Unlike Hybrid Capture 2 (HC2), care HPV test is less costly, requires less technology and time to process, therefore very suitable in low resource settings. [6, 7]

Visual Inspection with Acetic Acid (VIA)

VIA screening is the simplest method of screening with the lowest cost and relative ease of use. The approach does not require high technology and has been demonstrated to reduce the deaths of women in developing countries [7]. During VIA, 5% acetic acid or vinegar is applied to the cervical mucosa. Normal tissue is unaffected by vinegar wash, but abnormal cells including dysplastic and cancerous cells turn white. The screening method allows the practitioner to diagnose and treat abnormal cells almost immediately in a health center, typically using cryotherapy which is the application of liquid nitrogen or carbon nitrogen to the dysplastic area.

Cervical Cancer Vaccination

Studies indicate that preventive strategies to reduce cervical cancer incidence should focus on preventing risk factors. Another more recent preventive approach involves immunization. Women often become infected by HPV shortly after becoming sexually active. Eighty-seven percent of cases of cervical cancer are caused by 7 types of the 40 HPV genotypes that infect the vaginal tract [8]. However, 2 types, HPV 16 and HPV 18, are responsible for 70 percent of all cases [4]. Human papillomavirus (HPV), the acquired causative agent of most cervical cancer, is preventable by prophylactic vaccines [5]. The HPV vaccine has been available since 2006 and can prevent 70% of HPV-caused cervical cancers if the 3 dose vaccine series is completed. The series begins with one injection and is followed by a second 2 months later

and a third at the end of 6 months. The available vaccines are Quadrivalent Gardasil which prevents HPV 6, 11, 16, and 18 bivalent Cervarix, which prevents only HPV 16 and 18. The cost for 3 doses of the Quadrivalent Gardisil vaccine is $360 in the United States. Cervarix costs $240 in Canada for the recommended 3 dose regime (Canada Free Press, 2010). Few governments and even fewer women in developing countries can afford either drug. In 2011 Mexico, Panama and South Africa arranged to receive the Gardasil vaccine for US $40 [(4)].

In 2011, Rwanda was the world's first low-income country to provide universal access coverage for the HPV vaccine. Rwanda received an offer from Merck & Co. Inc. for 3 free years' coverage of the HPV vaccine [(9)]. The Gardasil Access Program (GAP) is managed by Axios Healthcare Development that distributes free HPV vaccines to organizations and institutions within eligible low-income countries as long as they are capable of covering all other costs related to the vaccination program, including transportation, storage, community outreach, distribution of the vaccine, and data collection [(1)].

The achievement of over 93% coverage of 3 doses of the HPV vaccine in Rwanda was made possible through school-based vaccine clinics, and community involvement in tracking and locating missing eligible enrolled and non-enrolled school girls. The prophylactic HPV vaccine offers new promise for primary prevention of cervical cancer. However, the HPV vaccine does not replace cervical screening. Immunization can be ineffective due to missing follow-up doses [(5)]. It is clear that education and resources are key components to all cervical cancer screening and prevention programs.

Challenges to cervical cancer screening in developing countries

The lack of screening and prevention for cervical cancer in developing countries has made it extremely challenging and difficult to decrease mortality rates. In developed countries where cytology-based cervical cancer screening is the standard of care, cervical intraepithelial

neoplasia is often detected and treated before the development of invasive cancer. The failure to adopt and implement an effective screening program in low-resource countries is due to a complexity of multiple barriers, including cost, lack of quality-assured infrastructure, non-available or untrained cytotechnologists or pathologists, and competing public health priorities such as communicable diseases. Based on finding on cervical cancer in multiple studies conducted by different international health organizations, the Alliance for Cervical Cancer Prevention (ACCP) was formed. ACCP supported development of alternatives to cytology that were more appropriate for low-resource settings (ACCP, 2011). Resulting programs were suitable for developing countries and were found to be cost-effective and have remarkably impacted the lives of many women [(6)].

Summary of Findings

Approach to cervical cancer screening

As seen before, in countries that have introduced successful cervical cancer screening programs, cervical cancer has become a relatively rare disease. In most developed countries, the Age Standardized Incidence Rate (ASIR) for cervical cancer is less than 10/100,000, whereas in developing countries, the ASIR of cervical cancer ranges from 25 to 55/100,000.[(3)]

Cytologic screening has led to vast improvements in prevention and early detection of cervical cancer. Evidence of the effectiveness of this approach has led to the adoption of cervical cytology screening in all developed and some developing nations. The standard approach to cervical cancer screening in developed settings is to use cytology, typically in some combination with HPV testing, followed by colposcopy, and then treatment based on

the results of colposcopic results. This approach proves too long because it requires three visits for communication of test results after each step.

Due to multiple barriers discussed below, the success of this approach used in developed countries has not been replicated in developing countries. Cytology-based screening programs require a relatively sophisticated and costly infrastructure, including highly trained personnel, built-in quality control, ongoing training of staff, adequately equipped laboratories, and functional referral systems to communicate results to the tested women. HPV testing is costly, and when used as a triage test, adds an extra processing step to cervical cytology. Additionally, colposcopy requires a level of clinical expertise typically found only in tertiary health care facilities, if available at all, and histology requires a laboratory infrastructure and trained pathologists, all of which are in short supply in poor countries.

A functional cervical cancer screening program in a low resource setting must include consideration of the screening test and its characteristics and also address the limitations of health care access and infrastructure. Ideal characteristics of a cervical cancer screening test used in such settings include:

- Can be performed in a primary health care facility
- Can be performed by trained nurses or paramedical staff, particularly where there are few or no physicians
- Requires little technology and staff training to perform, process, and interpret.

Performing screening and treatment at the same visit, thereby eliminating the intermediate steps of colposcopy and histological sampling, is another strategy that can avoid patient noncompliance with follow-up and reduce the overall costs of cervical cancer prevention.

Screening frequency and patient age

Women in developed countries are often screened for cervical cancer every one to three years. However, this screening frequency is not possible in most low resource settings. Decisions regarding screening frequency must be made based upon available resources. In programs in which women will receive screening only once or twice in a lifetime, screening should focus on the age range that will result in the largest reduction in cervical cancer incidence and mortality.

The greatest impact on cervical cancer reduction appears to result from screening women aged 30 to 39 years. This is supported by a subgroup analysis from a randomized trial in which over 80,000 women aged 30 to 59 in India were assigned to either VIA screening or cervical cancer health education. At seven-year follow-up, women in the screening group showed a significant decrease in age-standardized rates of cervical cancer incidence (25 percent) and mortality (35 percent); these decreases were greater in women aged 30 to 39 (incidence: 38 percent and mortality: 66 percent) compared with other age ranges (40 to 49 years: 18 and 45 percent; 50 to 59 years: 24 and 1 percent). **(11)**

Optimal screening frequency and patient age have also been calculated using modeling studies, since longitudinal clinical data are not available. One such modeling study used clinical data from India, Thailand, Kenya, South Africa, and Peru to evaluate cervical cancer screening in women once in a lifetime at the age of 35 years (11).

Alternative Methods to the cytology screening in Low Resource Countries

1. *Visual inspection with acetic acid*

Primary care clinicians or midlevel providers can be trained to perform visual inspection within a relatively short period of time; however, due to the subjective nature of the test, it is difficult to standardize quality control. Use of VIA screening followed by treatment reduces the rate of cervical cancer compared with no screening. This was illustrated by two large randomized trials: In one trial, clinics serving over 80,000 women aged 30 to 59 years in India were assigned to either VIA screening or cervical cancer health education [(11)].

Women with positive screening tests were further evaluated with colposcopy and directed biopsy, and those with Cervical Intraepithelial Neoplasia (CIN) were treated with cryotherapy or excision. At seven-year follow-up, women in the screening group versus the health education group showed a significant decrease in age-standardized rates of cervical cancer incidence (75 versus 99 per 100,000 person-years) and mortality (40 versus 57 per 100,000 person-years). [(11)]

Similarly, another trial included over 150,000 women aged 35 to 64 years in India who were assigned to either VIA screening or cancer education, performed by public health workers. The incidence of invasive cervical cancer was 26.74 per 100,000 in the screening group and 27.49 per 100,000 in the control group. At 12-year follow-up, the screening group showed a 31 percent reduction in cervical cancer mortality. A 7 percent reduction was also observed in all-cause mortality. [(12)]

The sensitivity and specificity of VIA in developing countries for detection of CIN or cervical cancer has been evaluated in multiple observational studies. The highest quality data are reported in a meta-analysis of 11 studies with over 58,000 women aged 25 to 64 years in India and Africa. Each woman underwent VIA and one or more other screening tests.

The reference standard was colposcopic-directed biopsy performed in all women. For detection of CIN 2 or a more severe abnormality (CIN2+), VIA had a sensitivity and specificity of 79 and 85 percent, respectively. [13]

2. HPV Testing

HPV testing used alone or in combination with VIA has the potential to improve cervical cancer screening in low resource settings. Unfortunately, it is not feasible to use the current HPV tests used in developed countries due to expense, the infrastructure required for processing, and waiting time for results. However, advances in HPV testing technology are under investigation with the goal of addressing these obstacles.

HPV testing reduces cervical cancer mortality in developing settings and is superior to VIA or cervical cytology. This was illustrated in a randomized trial of 131,746 women aged 30 to 59 years in rural India that compared a single lifetime screening with one of three screening modalities with standard care [14].

The screening modalities were: HPV testing using the Hybrid Capture 2 test [HC2], cervical cytology, or VIA. At eight-year follow-up, women who received HPV testing versus standard care had a 50 percent reduction in stage II or higher cervical cancer (15 versus 33 per 100,000 person-years) and cervical cancer mortality (13 versus 26 per 100,000 person-years). For the groups screened by cytology or VIA, rates of stage II or higher cervical cancer (VIA: 32 per 100,000 person-years; cytology: 23 per 100,000 person-years) or cervical cancer mortality (VIA: 21 per 100,000 person-years; cytology: 21 per 100,000 person-years) did not differ significantly compared with standard care, but were significantly higher than women in the HPV testing group. This result for VIA differed from the finding of the trial in 80,000 women described above; the authors attributed this difference to a higher rate of treatment in that trial. [11]

Rapid HPV Test

The HPV tests (e.g., HC2) used in developed countries are prohibitively expensive for low resource settings (in the United States the cost per test is approximately $50 to 100), and the waiting time for a result is one or more days. This is an additional impediment to patient follow-up. However, data are emerging regarding a new HPV test (care HPV) that is affordable, gives results quickly, and is portable. Each test will cost less than US $5, the processing kit has its own reagents and water supply and can be run using batteries, and the result is available within 2.5 hours. The new test detects 14 high-risk types of HPV, similar to the 14 or 18 types detected by the tests used in developed countries. This test is not yet commercially available. [15]

The rapid result HPV test appears to perform as well for the detection of high grade cervical neoplasia as standard HPV testing, and to be superior to VIA. The single study that has evaluated the rapid result test was a cross-sectional study of 2,388 women in China aged 30 to 54 years. Each woman was assessed with a self-collected vaginal specimen (for care HPV testing), VIA, and a provider-collected cervical specimen (for care HPV, HC2, and cervical cytology); colposcopic-directed biopsy was performed in women with suspicious lesions and used as the reference standard. HC2 testing showed no significant difference in detection of CIN2+ versus provider-collected care HPV, but was superior to self-collected care HPV (sensitivity and specificity, HC2: 97 and 86 percent; provider-care HPV: 90 and 84 percent; self-care HPV: 81 and 82 percent). Similarly, VIA was inferior to either a provider-collected or self-collected care HPV for detecting CIN2 + or high grade lesions (sensitivity and specificity, VIA: 41 and 95 percent). Direct comparison of collection method for care HPV

revealed no significant difference in high grade lesions detection between provider- and self-collected samples. [15]

These data are promising and indicate that rapid result HPV testing may be suitable for performing screening and treatment on the same day in low resource settings.

Increasing HPV test specificity

HPV testing has a high sensitivity, but a low specificity. Specificity takes added importance in low resource settings whether follow-up for a positive test is further evaluation or immediate treatment. Additional costs are incurred when women with false positive screening tests are referred for a costly test like colposcopy. Also, where treatment is performed based on a screening test, low test specificity may result in large numbers of women being treated unnecessarily. [16]

One approach to the low specificity of HPV testing is to change the definition of a positive test. In the case of HPV testing, the definition of a positive test can be varied by changing the positivity threshold (expressed as the ratio of light emission, i.e., relative light units [RLU] per positive control specimen. As for most tests, increasing the specificity results in a decrease in sensitivity. This was illustrated in a study of over 2900 women in South Africa in which detection of CIN2+ by HC2 at a threshold of >1 RLU/PC (the typical standard) had a sensitivity of 88 percent and specificity of 82 percent, while a threshold of >8 RLU/PC had a sensitivity of 79 percent and specificity of 90 percent [16].

Self-collected samples

For women who do not have access to a speculum examination or who are reluctant to undergo a pelvic examination, self-collected vaginal samples can be used for HPV testing. Women can collect samples from the vagina using a tampon or a cotton swab, cytobrush, or

cervicovaginal lavage. Self-collection can be performed under supervision at a clinic or at home. If a woman collects a sample at home, it is then placed in a collection tube with a transport medium and brought back to the clinic for processing.

Self-collected samples were compared with clinician-collected sampled in a meta-analysis of 18 studies with 5441 women in which women collected vaginal samples for HPV testing.

The analysis found a high concordance (0.87) between results of self- and physician-collected samples. Studies that evaluated acceptability reported that women preferred self- versus physician-sampling. A limitation of this analysis was that many of the included studies were conducted among a referral population of women with known or suspected cervical disease; therefore, a high HPV prevalence may impact the results [(17)].

Further study is needed to determine the best method of self-collection (e.g., swab, cervical brush, tampon). This question was addressed in an earlier meta-analysis, which included 12 of the same studies as the analysis described above and used physician-collected HPV samples as a reference standard. For seven studies that used a tampon, a cotton swab or a cytobrush, the pooled sensitivity and specificity for HPV detection were 78 and 90 percent. For three studies in which a tampon was used, the results are reported as a range of sensitivities (67 to 94 percent) and specificities (80 to 100 percent). These data do not allow comparison among the methods. [(18)]

Self-collected HPV testing (with a cervical brush) was compared with cervical cytology performed at a clinic in a randomized trial of 12,330 women in Mexico. The acceptability of self-collected HPV testing was high: 98 percent of women in the HPV testing group agreed to collect the sample and performed the testing, while 89 percent of those scheduled for a Pap test had the test performed. HPV testing had a higher sensitivity for detection of CIN2+ (relative sensitivity 2.9, 95% CI 2.0-4.1) and for invasive cancer (3.6, 95% CI 1.6-7.9).

The disadvantage of HPV testing was that more women underwent colposcopy and ultimately had negative findings: 28 percent in the HPV testing group compared to none in the cytology group. For CIN2+, the positive predictive value of HPV testing was 12.2 percent compared with 90.5 percent for cytology. [19]

Given these data, self-collection appears to be a useful method for HPV testing in women who do not have access to a speculum examination.

Combining two screening tests

Combining two screening tests (e.g., VIA and HPV testing) is one approach to balancing the strengths and weaknesses of each test. Two-test strategies can be either: additive, with screen positive defined as an abnormal result on either test considered screen positive, or sequential, in which only women with an abnormal result on the first test undergo a second test, and only those who are also positive on the second test would receive treatment. The goal is to maximize screening performance by combining a test with high sensitivity (e.g., VIA) with another test with high specificity (e.g., HPV testing with use of a high threshold for positivity).

Use of a two-test approach to screening increased specificity, but decreased sensitivity in a prospective observational study of 1266 South African women aged 35 to 65 years. Each woman underwent screening with Hybrid Capture 2 HPV testing and VIA with cervicography: a photograph of the cervix after application of acetic acid and cytology were also performed. Women with abnormal results on any of the screening tests underwent colposcopy at a follow-up visit. Based on study results, use of VIA or HPV alone would result in a missed diagnosis of CIN2+ in 6 or 8 per 1000 women screened, respectively, while 180 or 131 per 1000 would receive unnecessary treatment. Sequential use of VIA followed

by HPV would result in a missed CIN2+ diagnosis in 13 per 1000 women screened, while 41 per 1000 would receive unnecessary treatment. [20]

Given these results, it appears that it is preferable to use a combination of the two screening tests rather than either test alone. The number of missed diagnoses is notable, but does not outweigh the large decrease in the number of women who would receive unnecessary treatment. Complications are rare with cryotherapy, the predominant method of treatment for CIN used in developing settings. However, unnecessary treatment also incurs costs, which may reduce the number of total women who can be screened within a particular program. [20]

Screen and Treat Protocols

A screening test followed in the same visit by treatment of women with positive results is referred to as a "screen and treat" or “see and treat” protocol. This approach is only possible with screening tests that produce immediate results (e.g., visual inspection, rapid result HPV testing). One-visit protocol eliminates communication difficulties involved in delivering and interpreting written results for patients as well as the issue of noncompliance with follow-up, in contrast with protocols that require two visits (screening followed by treatment) or three visits (screening followed by colposcopy followed by treatment).

The ability of screen and treat protocols, specifically with use of HPV testing, to reduce the rate of high-grade CIN or cancer was demonstrated in a randomized trial of 6,555 previously unscreened women in South Africa, aged 35 to 65 years. All women were screened with VIA, HC2 HPV testing or cytology and were randomized to one of three groups: VIA screen positive followed by cryotherapy; HPV screen positive followed by cryotherapy; or no further evaluation or treatment for six months. All women also underwent HIV testing. At six-month follow-up, colposcopy with directed biopsy was performed in all women and

CIN2+ was found in significantly fewer women in both the VIA and HPV screen and treat groups (2.2 and 0.8 percent, respectively) versus the delayed group (3.6 percent). This difference persisted in a subset of 2,708 women who were evaluated at 12 months, with a rate of CIN2+ for VIA and HPV versus the delayed group of 2.9 and 1.4 percent versus 5.4 percent. [21]

Treatment based on results of screening tests with low specificity, such as VIA and HPV testing, will result in some women receiving unnecessary treatment. However, cryotherapy, the preferred treatment in developing settings, has a low complication rate. In this trial, adverse effects reported by women who underwent cryotherapy included vaginal discharge (78 percent), abdominal pain (30 percent), and abnormal bleeding (14 percent); only one woman had bleeding that required hospitalization. Women who underwent cryotherapy had more unscheduled visits during the study period than those who did not (1.0 versus 0.5 percent).

This study is limited by the protocol used, since screening was followed two to six days later by treatment in the screen and treat groups, while a one-visit approach is generally an important component of screen and treat protocols. In fact, 82 women did not return after the initial screening visit. [22]

There is another limitation to the protocol used in the study related to a serious ethical concern about the delayed treatment for women who tested positive. Hopefully, the HIV test offered to all women in the study has been used to screen and treat earlier the group of women at higher risk of cervical cancer who tested HIV positive and had abnormal screening findings.

Cost-effectiveness is also likely to be improved with one-visit screen and treat protocols than those requiring two or more visits. The data regarding cost derives from studies based on mathematical modeling rather than clinical studies. In one such report, based on a theoretical

cohort of previously unscreened 30 year-old black South African women, a single visit in which screen-positive VIA or HPV testing is coupled with cryotherapy would be more cost effective than two visit protocols with HPV or cytology (lifetime cost per woman US $39 to 41 versus $42 to 44).[20]

HPV Vaccines

Two vaccines are available for prevention of many HPV infections: One is the HPV quadrivalent vaccine: Gardasil from Merck &Co, targeting HPV types 16, 18, 6, and 11. The second, Cervarix, is a bivalent vaccine against HPV types 16 and 18: made by GlaxoSmithKline. Both vaccines were shown by randomized clinical trials to be highly effective in prevention of high-grade squamous dysplasia, especially in HPV-naïve populations (93% of protection) but also, to a lesser degree, in patients already exposed to HPV. Guidelines for use of the vaccines differ somewhat, but all recommend the vaccines be given to females no younger than 9 years, preferably before the onset of sexual activity. Each vaccine requires 3 doses with a total cost of at least $300. Ideally, HPV vaccines should be available in low-resource settings, but as the cost of the vaccine has been prohibitive, only limited demonstration projects using donated vaccine have been carried out in low-resource settings. [23, 24]

Cervical Cancer Challenges

We know that competing healthcare priorities constitute the first major barrier to screening in low income countries. For instance, each year almost 300,000 women in the world die from pregnancy related complications or childbirth, and more than 90% of them come from the developing world. The second barrier to screening is in relation to limited human and financial resources in poor countries where health facilities are limited, under-resourced or

overburdened. Low resource countries also have very limited cancer diagnostic, treatment and palliative care services. [25]

Another contributing factor to limited access to health care in poor countries is the urban/rural bias which is extreme in Sub-Saharan Africa where, for instance, more than 50% of people live more than 10 km from the nearest primary care center without any transportation facility. In this context, it is understandable that, in understaffed health facilities with shrinking public budgets, the practice of a Pap smear will be considered quite unnecessary, especially with its high cost estimated at $40 to $85. [26, 27]

I strongly agree with those who think that it would be more cost-effective to start screening women in developing countries at the age of 30-35 years as the yield in terms of disease detection is much greater in older women than in younger women. On average, it takes about 10-20 years for a cervical cancer to develop once a cervical cancer precursor is present. The following table shows the impact of cervical cancer screening on the cumulative incidence of cervical cancer, based on data collected from successful screening programs. These data were modeled based on screening women aged 35-65 years. [25, 27]

Table 1. Percentage-Cumulative reduction in cervical cancer among women (35-65) years

Interval for screening	Pap Tests performed (Number)	Cumulative reduction in cervical cancer (%)
Yearly	30	93
Three yearly	10	91
Five yearly	6	84
Ten yearly	3	67

Denny L. (2005)

Moreover, this approach differs from that currently used in developed countries, where screening by conventional Pap smear starting at 21years with a year or 3 years interval would benefit from 2 new screening tests which prove less expensive and adapted to low income countries : VIA, and HPV/DNA testing.

The VIA and HPV/DNA testing have the advantage of offering a screen and treat approach called "cryotherapy" aiming to suppress the cervical cancer precursors using the "cold effect". In addition, they are more appropriate and affordable as screening methods for low resource countries. A screening by VIA plus cryotherapy has been estimated to cost between $1.30 and $10 in studies conducted in Kenya, Ghana and South Africa. As for the HPV-DNA (*careHPV*), its cost is estimated at $5 per test. Like the Pap smear in developed countries, screening programs using these 2 low cost tests hopefully will help reduce the incidence of cervical cancer by removing disease precursors before they develop into cancer. High coverage has been shown to be much more important than frequency of screening. For instance, a 10 yearly screening program with a high population coverage can yield a two thirds reduction in cervical cancer. [26, 27]

The primary prevention strategy could help to eliminate the cervical cancer if it is well applied in low income countries. Although Cervarix and Gardasil protect efficiently against infection with HPV types 16 and 18, these vaccines do not protect against HPV types found in approximately 30% of cervical cancers. Consequently, even women who have been vaccinated need to continue to have regular Pap smears [8].

Experience with the Rwanda Cervical Cancer Prevention Program

In 2009 a technical meeting between the Rwandan Ministry of Health (MoH) and Merck & Co. sparked a partnership for the national rollout of the HPV vaccine in Rwanda. Merck

agreed to donate approximately 2 million doses of Gardasil over a period of three years and to guarantee concessional pricing of the vaccine to Rwanda and external funders thereafter. Simultaneously, the health ministry initiated the planning phase for a comprehensive national program for cervical cancer prevention, screening and treatment. It is worthwhile to note that Rwanda had already achieved coverage rates exceeding 93% of eligible subjects for vaccines against nine childhood diseases, including the pneumococcal conjugate vaccine.

Encouraged by this immunization success, Rwanda elected to provide HPV vaccine to all girls in grade 6 of primary school, for free, on three designated "health days" each year, beginning in 2011. In November 2011, the first HPV vaccine dose was given to the first cohort of girls. Because 98% Rwandan girls attend primary school, implementers felt that the highest coverage could be attained through schools. **(9)**

By enlisting teachers and village leaders in sensitization efforts and by mobilizing the country's 45,000 community health workers to trace out-of-school girls, the HPV vaccination program achieved a high coverage rate in its first year: 92,107 (93.2%) of the 98,792 eligible girls identified in 2011 were fully vaccinated (Table 2). Two "catch-up" rounds of vaccination targeted girls who were in the third year of secondary school in 2012 or 2013. The aim was to ensure that all girls younger than 15 years in 2011 had the opportunity to receive a full course of HPV vaccination. In 2012, the routine campaign targeting girls in grade 6 of primary school led to 90,188 of the 93,243 eligible girls each receiving three doses, while 394 of 549 out-of-school girls aged 12 years were also fully vaccinated. The corresponding "catch-up" campaign – targeting girls in the third year of secondary school – led to the full vaccination of 43,927 of 45,361 eligible in-school girls and 630 of 815 eligible out-of-school girls aged 14 years. The table 2 gives a total of 135,139 (96.6%) of 139,968 eligible girls fully vaccinated in 2012. **(9)**

Table 2. Human papillomavirus (HPV) vaccination coverage, Rwanda, 2011–2012.

Coverage	**2011**			**2012**		
	Round 1	**Round 2**	**Round 3**	**Round 1**	**Round 2**	**Round 3**
Girls vaccinated						
In school	91 752	89 704	88 927	137 147	134 645	134 115
Outside school	2 136	3 066	3 180	1 162	845	1 024
Overall	93 888	92 770	92 107	138 309	135 490	135 139
Cumulative coverage (%)	**95.0**	**93.9**	**93.2**	**98.8**	**96.8**	**96.6**

Binagwaho et al., (2012)

There has been concern that some countries that are eligible for support from the Global Alliance for Vaccines and Immunization (GAVI) may lack sufficient capacity to plan adequately, manage cold chain deployment, navigate the nuances of communication, achieve high coverage and mobilize partners to ensure financial sustainability. [(9)] Rwanda's experience and success in scaling up access to HPV vaccine indicates that these concerns are largely unfounded.

Halfway through the first year of Rwanda's HPV vaccination program, Merck dropped the price of the HPV vaccine by more than 70% from its previous lowest price per dose – from 16.95 to 5.00 United States dollars. Following GAVI's incorporation of the HPV vaccine into its routine funding portfolio in late 2012, further price reductions have been announced, with more expected in the near future. Merck's partnership helped to bridge the gap between Rwanda's aspirations for the prevention of cervical cancer and the actions that the country was able to implement against the disease.

The good news is that private sector pharmaceutical and medical device companies have recently declared an interest in Rwanda's program against cervical cancer. In late 2011, for

example, Qiagen signed a memorandum of understanding with the Rwandan Ministry of Health and agreed to donate equipment and consumables for HPV screening, beginning in 2013.

Before the implementation of the national strategic plan for cervical cancer prevention, care and control, some Pap smear tests and visual inspection of the cervix with acetic acid were offered sporadically at several public and private health facilities across Rwanda[(28)]. Now with the equipment and consumables donated by Qiagen, Rwanda has planned to scale up access to more screening options in five district hospitals and 15 health centres in these hospitals' catchment areas beginning in June 2013. If everything goes according to plan, cervical cancer screening in Rwanda will be decentralized to 30 public hospitals and nearly 100 health centres by 2015. Between 2013 and 2016, Qiagen will donate 250 000 assays and 29 machines for its *careHPV/DNA* testing system, while the Rwandan government and other partners will finance the scale-up of visual inspection of the cervix with acetic acid.

Since December 2012, nurses and physicians performing the screening tests have been receiving intensive training. Eight national pathology trainers will be trained by the American Society for Clinical Pathology, and QIAGEN has already trained eight laboratory technicians as trainers in reading the results of tests for HPV/DNA and histopathology. These 16 trainers will together train another 32 pathologists and laboratory technicians by the end of 2013. The National Reference Laboratory in Kigali will receive technical support to assume full responsibility for diagnosing cervical cancer by 2015.

Starting in June 2013, at standard meetings with nurses in Rwanda's 15,000 villages, community health workers will be told the dates when a mobile team of one physician and two to four nurses will visit the local health centre for HPV screening over a three-day period. The community health workers will enroll women for free screening and then return

the corresponding enrolment forms to the local health centre. The ages of the women enrolled will depend on whether they have been found infected with human immunodeficiency virus (HIV). Women known to be HIV-positive and aged 30 to 50 years will be enrolled, as well as other women aged 35 to 45 years. Nurses will then report to the district level, indicating the number of women enrolled for each screening day. These reports will allow the mobile teams to determine the quantity of reagents needed and the likely duration of the screening on each screening day. With this system, it is expected that approximately 360 women will be tested in a single day by each team. Each screened woman will be asked to stay at the health centre for a few hours, until the results of her test are available. While waiting, she will be educated about cervical cancer and other aspects of reproductive health. **(9)**

For the precancerous lesions treatment, Rwanda has chosen to focus first on cryotherapy and LEEP. These two procedures will be provided for free on an outpatient basis. Cryotherapy will be available at health centres and hospitals, whereas LEEP will be only available in hospitals. If a woman requires more involved treatment for cervical cancer, such as surgery, chemotherapy or radiotherapy, she will be immediately referred for further management: colposcopy, biopsy and necessary comprehensive treatment at the tertiary level. Finally as part of the Rwanda Human Resources for Health Program, in collaboration with a consortium of US universities, it is hoped that the Faculty of Medicine of the National University of Rwanda will train more nurses, gynecologists, pathologists and radiation oncologists who will be instrumental in carrying out the National Cervical Cancer Program. **(9)**

Conceptual Framework for Cervical Cancer Prevention

Cervical cancer is a preventable disease and curable disease if detected early; however, in order to minimize cervical cancer screening barriers in low resource settings, strategies should be socially and culturally acceptable, and health professionals should be quite knowledgeable and trustworthy in their procedures to gain collaboration from their clients and various community groups.

A conceptual model targeting health behavior change could be useful, and we know that a health-seeking behavior is largely influenced by different barriers including perceived risks and seriousness of the disease as well as the perceived individual susceptibility. At the individual level, education is the most important key for cervical cancer prevention. It is known that health literacy is essential for individual participation in health education. Thus the success of the prevention program will come from the education and empowerment of women. Understanding cervical cancer and the screening process requires women to have a basic understanding of their internal and external anatomy as well as basic physiologic processes.

Women need not only a general basic education but also adequate counseling for an awareness prompting them to seek out cervical cancer screening for themselves and HPV vaccination for their young girls. At the community level, teams in the MoH in charge of Information, Education and Communication in each country, should find a way to delivery health messages at schools through mass media and community mobilization about cervical cancer cofactors such as smoking and other sexual transmitted diseases including HIV.

Education will help also to address the various myths and cultural beliefs associated with cervical cancer and cancer in general because, in most communities in Africa for example, the diagnosis of cancer amounts to death. At the household level, the husband and especially

the female children must be informed in order to obtain their active participation in the campaign against cervical cancer.

It would be challenging to attempt to change health behaviors of any specific population without the participation of the religious and administrative leaders in the community. Also, the negative cultural beliefs and attitudes will be more easily addressed with full awareness of the cervical cancer damage on the part of the influential women's community group.

Finally the issue of healthcare system dysfunctionality including the lack of staff and supplies should be seriously addressed as seen in the Rwandan case program by the national Governments through the partnership with the public and private international foundations and organizations. (See Fig.3.)

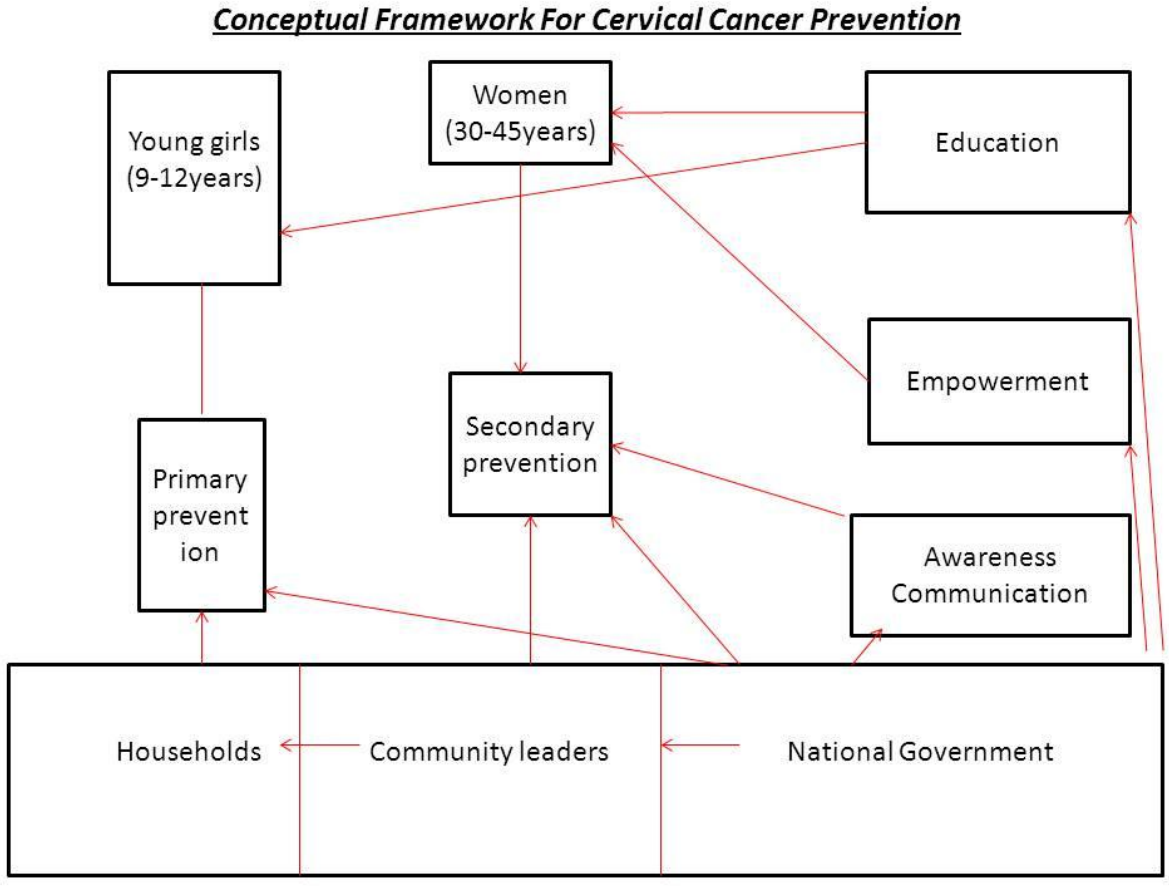

Fig 3. Conceptual Framework for Cervical Cancer Prevention in Low Resource Countries.

Conclusion

In a nutshell, to prevent successfully cervical cancer in low resource countries, the following requirements are essential:

- Vaccination of young girls before they contract HPV infection between 9 and 12 years
- Education of all intervening parties in the vaccination program: parents, teachers, media, community leaders
- Making available low cost technology for screening the majority of at risk women, preferably after 30-35 years.
- Increase funding for cervical cancer in low resourced countries with a high priority such as is the case for HIV/AIDS, and possibly in a combined program for the two diseases.

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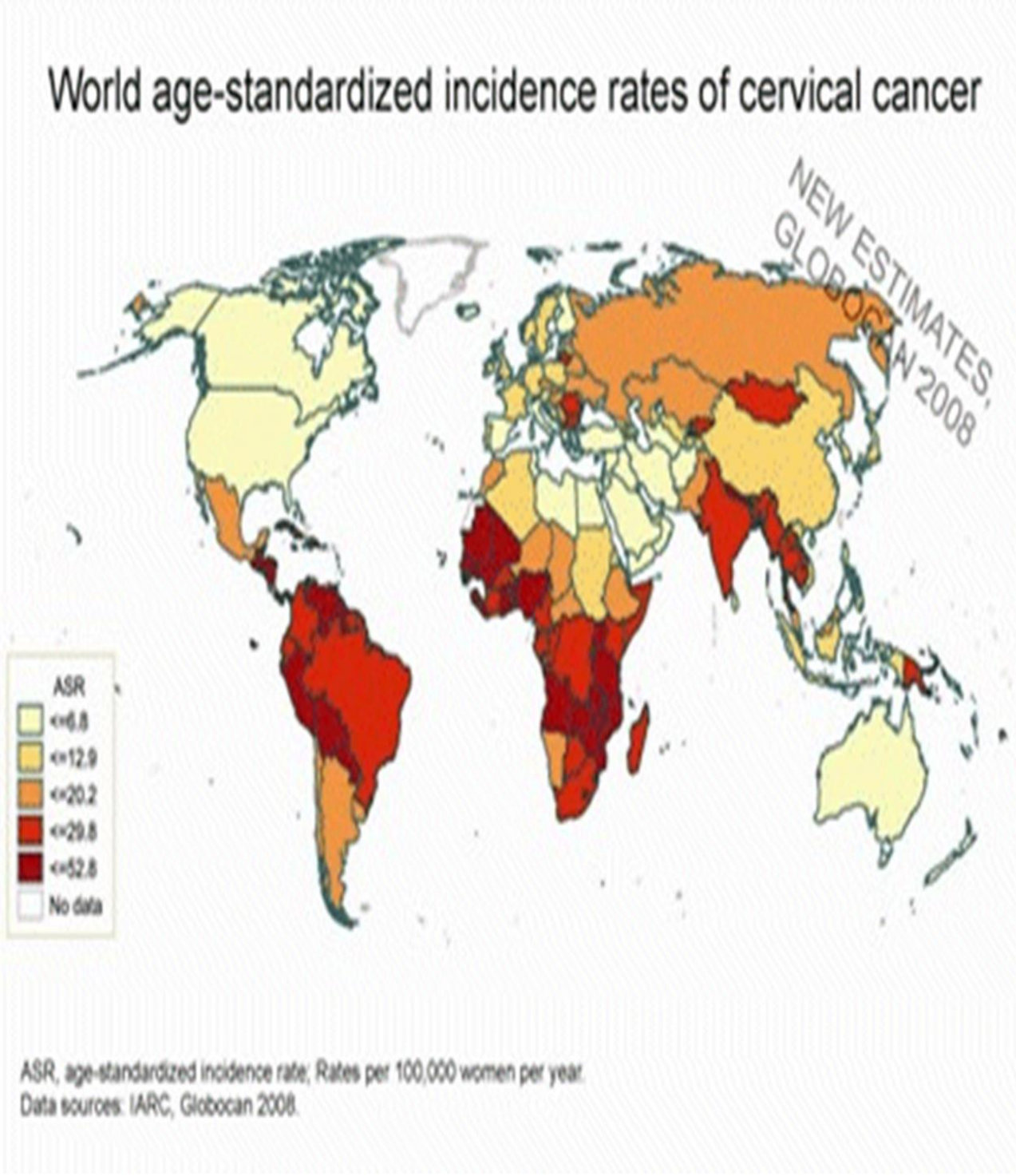
Appendix


World age-standardized incidence rates of cervical cancer
NEW ESTIMATES, GLOBOCAN 2008
ASR
<=6.8
<=12.9
<=20.2
<=29.8
<=52.8
No data
ASR, age-standardized incidence rate; Rates per 100,000 women per year.
Data sources: IARC, Globocan 2008.